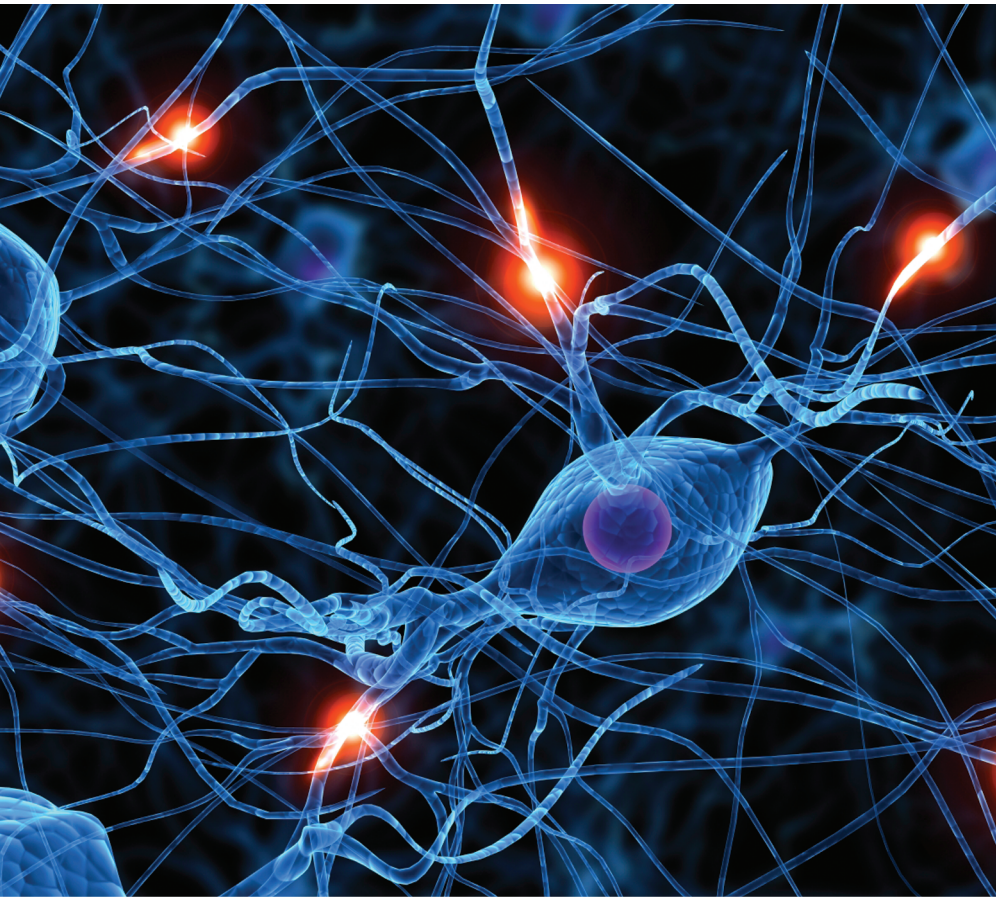
Update on Blood Brain Barrier



ROLE OF CHOLINERGIC SYSTEM AND CALCIUM SYNCHRONIZATION IN SCHIZOPHRENIA

by Atmaram Yarlagadda, MD, and Anita H. Clayton, MD

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ABSTRACT

A considerable body of evidence exists in the literature regarding impairment of signal-to-noise ratio in schizophrenia. The pathophysiologic role of cholinergic systems via calcium release and acetylcholine's involvement precedes dopamine regulation in processing information. We therefore hypothesize that acetylcholine dysregulation precedes dopamine dysregulation in schizophrenia. This is an earlier step associated with reception of the initial signal prior to the processing of a received signal by dopamine in the prefrontal cortex. The cholinergic system has a major impact on cognitive abilities, especially learning and memory, through acetylcholine. Reception and relay of sensory information through the process of arousal along the corticothalamic tracts to accomplish higher-level decision-making functions via acetylcholine is well established. The uncoupling of the received information (the signal) from the transfer of that information (the relay) to higher attentional and executive functions for processing of that information (the assembly) may possibly lead to altered perception.

KEY WORDS

blood brain barrier, cholinergic system, calcium synchronization, schizophrenia

INTRODUCTION

Neurophysiology research has made significant progress over the years, from cellular to molecular and currently transforming into nano molecular concepts. The concept of plasticity evolved from a complex, anatomic network of neurons joined by synaptic connections through dendrites and axons encased by myelin sheath and driven by physiologic electromagnetic forces. This process was first described by Charles Scott Sherrington.[1] Signal-to-noise ratio (SNR) impairment is now emerging as a phenomenon in the pathology of schizophrenia, especially considering the elevated P50 S2/S1 ratio in patients with schizophrenia and their relatives.[2,3] The hypothesis focuses on cholinergic, GABAergic, and glutaminergic neurons and their roles in synchronized calcium oscillations in the context of SNR impairment.

BACKGROUND

Perceptions can be normal or altered and are contingent on both anatomic and physiological factors. Alterations in perceptions of wakefulness, dreams, and hallucinations can be the result of macro- or microcircuitry deficits in the central nervous system (CNS). Deficits in macrocircuitry become apparent by using current technological advances such as neuroimaging. However, in most neuropsychiatric disorders, gross deficits are not apparent, especially when microcircuits are involved.[4] To understand microcircuitry and its impacton perceptions more fully, we should start at the initial signal or the sensory input received by the hypothalamic nuclei and its transfer to cortical layers prior to assembly and output manifested by higher functioning. The neurotransmitter acetylcholine is directly involved in these initial arousal mechanisms. Acetylcholine release by the stimulus from sensory afferents has a unique bimodal excitatory role on glutaminergic and GABAergic neurons.[5] These changes are reflected in the dynamics of action potentials generated in response to neurophysiological demands.

BASICS

To understand neuronal signaling mechanisms, we start with action potentials, resting potentials, and oscillations. Neurons consist of A) a cell body or the soma, like any other cell, with B) dendritic branches that serve as receptor sites for transmission of electrical activity from other neurons, which regenerate themselves at the C) axon hillock, a site free of synaptic input from which this electrical activity travels down to the D) cell axon, wrapped intermittently by a myelin sheath with unmyelinated breaks in between called E) *nodes of Ranvier* where sodium enters. Entry of sodium is rapid, triggering electrical activity. This initiates the depolarization wave leading to the action potential. Firing of action potentials is based primarily on the electrical charge in the axon hillock. A neuron reaches the threshold for action potential at around -50 millivolts (mv) as compared to the resting potential, which is at -70mv. Resting potential, therefore, is a state where the inside of a neuronal cell has more of a negative charge than the outside. Electrical activity required to predict an action potential is propagated by synaptic connections/dendrites between neurons in a process called *spatial summation* or through axons by temporal summation.

Neurons can take on an excitory or inhibitory rolein the CNS, depending on the proximity to the cell body or soma.[6] One of the factors influencing the excitation and inhibition funtion is blood perfusion to the neuron. According to literature, every neuron is perfused by a microvascular vessel, and these microvascular vessels comprise blood brain barrier (BBB).[7] Oscillations or perturbations occur when a neuron reaches the threshold for firing and an action potential is generated, resulting in abrupt changes in the cellular electromagnetic fields. Therefore, oscillations occur by discharge of the electromagnetic field immediately after firing of an action potential and are extremely sensitive to the integrity of BBB. Calcium plays a dominant role in the generation of oscillations via acetylcholine.[8] Corticothalamic neurons representing corticothalamic circuits have intrinsic resonance and self-organizational capabilities around 40 hertz (Hz) (gamma frequency range). At 40Hz, these neurons are capable of firing rhythmic-tuned action potentials in response to sensory afferents. These oscillations are considered normal and are thought to underlie conscious experience in dreaming. They are also recorded concurrently with hallucinations.[9–12]

According to one study,[13] hallucinations can arise whenever sensory input fails to adequately impact on intrinsic thalamocortical activity, allowing attentional factors to determine the content of perceptual experience in a manner that is unrestricted by sensory input.

DISCUSSION

Gamma oscillations have to be considered when exploring SNR impairment mechanisms in schizophrenia. Anatomic and physiologic factors at a cellular level (e.g., the integrity of the BBB) become critical to understanding the oscillatory mechanisms. This is different from the conventional focus of variations in normal physiological function starting with neurotransmission of dopamine.

Two types of action-potential firing modes have been described in the corticothalamic tracts: (A) synchronized tonic-firing mode, which is a partly depolarized state attributed to the wakeful/conscious state (e.g., in response to afferent stimulus or arousal comprising single-action potentials) and (B) desynchronized burst-firing mode, with trains of action potentials associated with inattentiveness and drowsiness (e.g., inhibitory, also occurring during slow-wave sleep [SWS]).[14]

Although there is lack of evidence associating the firing modes with diurnal variations, there appears to be a connection between the two phenomena. Synchronized

oscillatory rhythms emerge from excitory input to both glutaminergic and GABAergic neurons. *In-vitro* synchronization mechanisms using agonist and antagonist agents of acetylcholine were tested and established experimentally in slices of corticothalamic neurons. The findings reportedly were very close to *in-vivo* mechanisms.[15–17]

Desynchronization, which is a misnomer, is an exclusively inhibitory mechanism by gamma-amino-butyric acid (GABA) of the reticular thalamic nucleus via n-acetylcholine receptors (nACHR) suppressing background noise during wakefulness.[18]
In schizophrenia, there appears to be an uncoupling of the synchronization/desynchronization mechanisms due to compromise of the BBB with possible domination of synchronized oscillations (e.g., increased attentional activity causing impairment in the SNR ratio).[13] Desynchronization abnormalities tend to improve after smoking or after brief periods of SWS in patients with schizophrenia, suggesting a possible restoration of the oscillatory balance by stimulating the nicotinic acetylcholine receptors (nACHR). Incidentally, administration of nicotine via nACHRs restores amplitude suppression of P50 in response to S2 in patients with schizophrenia and in their relatives.[19,20]

Role of calcium. Rises in cytosolic calcium have been noted in both tonic- and burst-firing modes. However, the rise of calcium in tonic mode seems to be slow and reduced with generation of single-action potentials as compared to burst-firing mode with trains of action potentials.[8] Increases in calcium levels are reported in both the soma and nucleus of the neurons. It is now established that increased nuclear calcium levels can induce gene transcription, especially those associated with learning and memory tasks in the hippocampus.[21,22] In the context of tonic and burst firings, one can only postulate that gene transcription mechanisms occur during attentional states by increasing the involvement of rhythmic synchronized oscillations.

N-methyl-D-aspartic acid (NMDA) receptor hypofunction resulting in glutaminergic excitotoxicity, as previously described in schizophrenia research, combined with acetylcholine-induced glutaminergic hyperactivity could potentially raise the cytosolic calcium to elevated levels.[23] Consequently, hypercalcemia could worsen the signaling process in schizophrenia by destabilizing synchronization and desynchronization mechanisms. The increased calcium signaling, also known as perturbations, has recorded in schizophrenia using a computational mathematical model called the Boolean network along with D1/D2 receptor-generated perturbations.[24]

These perturbations or intensified calcium-generated oscillations may promote impaired SNR in alignment with the preexisting P-50/S2 defects in schizophrenia.[8]

The central role of calcium starts with the reception of a signal by hypothalamic nuclei via acetylcholine and continues with the processing of information into assemblies by dopamine in higher functioning areas, such as the prefrontal cortex, and as a calcium-induced calcium release (CICR) InP3. This central role highlights the unifying effects[25,26] of calcium in the regulatory mechanisms of schizophrenia. Therefore, we hypothesize that acetylcholine's role in the pathophysiology of schizophrenia via calcium influx deserves a closer look in addition to dopamine's involvement.

PROPOSED INTERVENTIONS

Recent discovery of the calcium homeostasis modulator gene 1 (CALHM1) in AD27 and the role of CICR for cross-talk in neuron networks[28] are critical in the search and development of CNS calcium homeostasis modulators. For example, modulators at the neurotransmitter level involving acetylcholine could be explored in select schizophrenia cases. Other potential candidates include nACHR modulators with chloride channels, as well as potassium activity since acetylcholine is known to regulate GABA production via this route.[29]
The following are a few examples of existing medications that are not currently indicated as adjuncts in the treatment of schizophrenia: dantrolene, L-type calcium channel blockers (nimodipine), donepezil (Aricept®), and the NMDA receptor antagonist memantine (Namenda®).

According to one study, dantrolene inhibited Ca2+ mobilization using hippocampal and cerebellar granule cells affecting frontal cortical cells. In addition to significantly affecting NMDA or KCL-induced Ca2+ response, dantrolene acts even in the presence of antagonists. The authors also state that it may effectively influence spontaneous Ca2+ oscillations.[30] Currently this muscle relaxant is used only in the treatment of neuroleptic malignant syndrome; however, it could be studied further and potentially used in conjunction with first generation antipsychotics.

L-type calcium channel blockers (CCB), such as nimodipine, a CCB that works at the slow calcium entry phase of the action potential,

are mainly used during cerebrovascular accidents (CVA).[31] With no reported side effects, this particular CNS calcium channel blocker should be studied in clinical trials especially in context of CVA and antipsychotic use in the elderly.[32]

Donepezil is a well known treatment for Alzheimer's disease. It is known to improve cognitive functioning by enhancing the levels of acetylcholine. In schizophrenia, one concern is for cognitive deterioration or "downward spiral." However, there are no known clinical trials of donepezil in schizophrenia; therefore, donepezil should be examined to ascertain its effects in patients with negative symptoms.

Memantine is another medication currently used for the treatment of Alzheimer's disease. It acts at the NMDA receptor site regulating glutamate, which potentially could also influence cytosolic and nuclear calcium levels.[33]

Lastly, by modulating nuclear calcium levels, the forward cascade of excitotoxicity and unwarranted gene expression could be prevented by the above referenced medications.[34] Calcium homeostasis modulators are not currently available; to pursue *in-vivo* trials, experimental studies are needed to test their role in CNS.

The BBB has a significant role in various psychopathologies at different locations in the CNS. Although possible, site-specific delivery of medications to the CNS remains complicated.

CONCLUSION

The etiology of neuropsychiatric disorders is multifactorial, and clearly an overlap of symptoms exists (i.e., psychosis in dementia and cognitive deficits in psychosis). If dementia improves with acetylcholine modulation, clearly the same should apply to cognitive deficits in schizophrenia. Therefore, as practicing psychiatrists, our treatment strategies should not be limited to any single class of psychotropics; rather, we should incorporate a broader psychopharmaceutical approach aimed at preventing the overall progression of the condition.

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AUTHOR AFFILIATIONS: Dr. Yarlagadda is from Newport News, Virginia, and Dr. Clayton is Professor, Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, Virginia.

ADDRESS CORRESPONDENCE TO: Atmaram Yarlagadda, MD; E-mail: atma@golfolks.com